REMARKS

Applicants have studied the Office Action, and have cancelled all claims and presented new claims in response thereto. It is respectfully submitted that the application, as amended, is in condition for allowance. Prior to entry of the present amendment, claims 12-14, 16-30 and 56-99 were pending in the present application. Claims 1-99 have been cancelled by virtue of the present amendment, and new claims 100-130 have been added. No new matter has been added. Reconsideration and allowance of the claims in view of the foregoing amendment and the ensuing remarks are respectfully requested.

New claims 100-109 are substantively similar to cancelled claims 12-14, 16-20 and 23-25, but are specifically directed to the treatment of irritable bowel syndrome. Support for these claims may be found throughout the specification, for example at page 23, lines 15-24, as well as in claims 12-14, 16-20 and 23-25 as originally filed in the present application.

New claims 110-119 are substantively similar to cancelled claims 12-14, 16-20 and 23-25, but are specifically directed to the treatment of fibromyalgia. Support for these claims may be found throughout the specification, for example at page 23, lines 15-24, as well as in claims 12-14, 16-20 and 23-25 as originally filed in the present application.

New claims 120-129 are substantively similar to cancelled claims 12-14, 16-20 and 23-25, but are specifically directed to the treatment of Crohn's disease. Support for these claims may be found throughout the specification, for example at page 29, lines 8-12, as well as in claims 12-14, 16-20 and 23-25 as originally filed in the present application.

New claim 103 is substantively similar to cancelled claim 12, but is specifically directed to the treatment of conditions such as chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder and multiple sclerosis. Support for this claim may be found throughout the specification, for example at page 23, lines 15-24, as well as in claim 12 as originally filed in the present application.

In the Office Action, the Examiner rejected claims 12-14, 16-30 and 56-99 under 35 U.S.C. § 112, first paragraph, "*because the specification, while being enabling for methods of treatment of bacterial overgrowth comprising detecting small intestinal bacterial overgrowth and at least*

partially eradicating the bacterial overgrowth, does not reasonably provide enablement for treatment of the diseases recited in the claims." Applicants respectfully submit that this rejection has been rendered moot by virtue of the cancellation of claims 12-14, 16-30 and 56-99 in the present amendment. However, Applicants were mindful of this rejection when drafting their new claims, which are directed to specific conditions, such as irritable bowel syndrome and fibromyalgia, and offer the following remarks in support of the allowability of the newly presented claims.

In the Office Action, the Examiner stated that the instant application is enabled for methods of detecting small intestinal bacterial overgrowth and partially eradicating the bacterial overgrowth, but that it is not enabled for methods of treating the recited conditions. As support, the Examiner cited the In re Wands "undue experimentation" factors and, in particular, argued that the specification lacks working examples and that the art field is unpredictable because the recited conditions are of unknown etiology.

As an initial matter, the enablement standard does not require the Applicants to demonstrate that the claimed invention in fact works; actual reduction to practice is not necessary prior to filing. Gould v. Quigg, 822 F.2d 1074, 1078 (Fed. Cir. 1987); MPEP § 2164.02. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims, then the enablement requirement of 35 U.S.C. § 112 is satisfied." In re Fisher, 427 F.2d 833, 839 (CCPA 1970); MPEP § 2164.01(b).

Here, the specification clearly discloses that the claimed methods may be practiced by detecting the presence of small intestinal bacterial overgrowth in a subject with a suspected diagnosis of one of the recited conditions, and by administering an antimicrobial agent, a probiotic agent or a prokinetic agent to at least partially eradicate the bacterial overgrowth and treat the condition. The claimed methods, far from requiring undue experimentation, are actually quite simple to test, and can certainly be practiced by one of skill in the highly specialized medical arts of treating the recited conditions. Merely by way of example, pages 21 and 22 of the specification teach that known methods of detecting bacterial overgrowth may be practiced in a patient that has a suspected diagnosis of, *inter alia*, irritable bowel syndrome. Pages 23 and 24 of the specification then teach that the bacterial overgrowth may be at least partially eradicated by the known and easily-practiced method of administering an antibiotic, thereby improving the symptoms of, *inter alia*, irritable bowel

syndrome, as described on page 29 of the specification. Thus, a practitioner of the relevant medical art would not need to engage in undue experimentation to test the methods recited in the newly presented claims. Instead, such a practitioner could carry out well-known steps and observe whether the condition of interest had thereby been improved.

Examiner has also cited a lack of working examples that demonstrate treatment of the various recited conditions. Applicants respectfully point out that compliance with the enablement requirement of 35 U.S.C. § 112 does not require the disclosure of working examples. As noted above, actual reduction to practice is not required for an application to be enabled. Accordingly, the Gould court held that "[t]he mere fact that something has not been previously done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. Gould, 822 F.2d 1078; MPEP § 2164.02. Thus, the lack of working examples cannot be used as an independent basis for rejecting a claim on enablement grounds; indeed, an invention is enabled if it is otherwise disclosed in a manner allowing one skilled in the art to practice it without undue experimentation. In re Borkowski, 422 F.2d 904, 908 (CCPA 1970); MPEP § 2164.02. In the instant application, a lack of working examples should not form a basis for rejection because, as shown above, the invention is disclosed in a manner well within the purview of one skilled in the highly specialized medical arts of treating the various conditions.

Notwithstanding the above, the Applicants acknowledge that working examples may be useful in a case involving an unpredictable art. Applicants further acknowledge that the Examiner has stated in the Office Action that the subject matter of this application is an unpredictable art because of the alleged unknown etiology of the various recited conditions. Applicants address the alleged unpredictable nature of the present art below, but first note that the present application does, in fact, contain several examples of experiments that were actually performed. Example 3, found on pages 31 and 32 of the specification, demonstrates detection and at least partial eradication of small intestinal bacterial overgrowth, accompanied by improvement of symptoms of irritable bowel syndrome. Example 6, found on pages 37 and 38 of the specification, demonstrates a similar effect for Crohn's disease, while Example 4, found on pages 33 and 34, provides experimental data for the recited methods in the case of fibromyalgia. Finally, Examples 4 and 5, found on pages 34 through 37, provide data generated for the claimed methods in chronic fatigue syndrome, depression,

attention deficit/hyperactivity disorder and multiple sclerosis. Applicants do acknowledge that a substantial portion of their data is directed toward irritable bowel syndrome. However, Applicants' data directed to the other recited conditions should not be undercut, particularly because that data demonstrates actual reduction to practice of the claimed methods; each of the examples demonstrates detection of small intestinal bacterial overgrowth, partial eradication of the bacterial overgrowth and improvement of the subject conditions. If the Examiner doubts the validity of the experimental results presented in the specification, Applicants respectfully submit that such a concern does not represent proper grounds for an enablement rejection. Thus, while Applicants maintain that working examples are not required to enable the presently claimed invention, Applicants respectfully note the presence of *actual* examples of experimental data in multiple locations in the specification.

The Examiner has also stressed the unpredictability of the art in rejecting the previously pending claims on enablement grounds. As support for that proposition, the Examiner has cited various publications that set forth that the recited conditions are of unknown etiology and has concluded that undue experimentation would be required to practice Applicants' invention. The Examiner essentially argues that because the various conditions are of unknown etiology, it cannot be demonstrated that they are linked to small intestinal bacterial overgrowth. Therefore, it cannot be shown that the conditions can be treated by at least partially eradicating small intestinal bacterial overgrowth. Thus, undue experimentation would be required to practice Applicants' invention.

It is true that some experimentation may be required to practice the present invention, although the amount of experimentation, as demonstrated above, would be minimal for one skilled in the art. However, experimentation is permissible and is not a bar to enablement. Wands itself holds that even "a considerable amount of experimentation is permissible, if it is merely routine." In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP § 2164.01. While Applicants maintain that only minimal experimentation would be required to test the presently claimed invention, it is undoubtedly the case that no matter how much experimentation is required, it can only be viewed as routine for one skilled in the relevant art. A medical practitioner would only need to practice a known method for testing for small intestinal bacterial overgrowth and then practice a known method for administering an antibiotic, probiotic or prokinetic agent, followed by a simple observation of whether a patient's symptoms of one of the recited conditions had improved.

Furthermore, Applicants respectfully submit that the art is not unpredictable since several publications have shown a link between small intestinal bacterial overgrowth, and/or intestinal infection, and the various recited conditions. For example, the Applicants have published several articles demonstrating a link between small intestinal bacterial overgrowth and irritable bowel syndrome. E.g., Pimentel, Mark et al., "*Methane Production During Lactulose Breath Test is Associated with Gastrointestinal Disease Presentation*," Digestive Diseases and Sciences, Vol. 48, No. 1 (January 2003), pp.86-92 (Exhibit A). The Applicants have also demonstrated an association between small intestinal bacterial overgrowth and fibromyalgia. Pimentel, Mark et al., "*Small Intestinal Bacterial Overgrowth: A Possible Association with Fibromyalgia*," Journal of Musculoskeletal Pain, Vol. 9, No. 3 (2001), pp.107-113 (Exhibit B). In addition, the present specification, at page 9, lines 18-24 cites suggested links between intestinal infection and Crohn's disease and discusses, at pages 11-12, a known method of treatment of Crohn's disease that involves eradicating bacterial growth.

Thus, Applicants respectfully submit, particularly with respect to irritable bowel syndrome, fibromyalgia and Crohn's disease, that the art is, in fact, predictable.. Since there is a demonstrated link between small intestinal bacterial overgrowth or intestinal infection and these conditions, the claimed methods can be easily and logically tested and cannot be said to be unpredictable.

..../12

Applicants believe that the foregoing amendments place the application in condition for allowance, and a favorable action is respectfully requested. If for any reason Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 488-7100 to discuss the steps necessary for placing the application in condition for allowance should Examiner believe that such a telephone conference would advance prosecution of the application.

Respectfully submitted,

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Methane Production During Lactulose Breath Test Is Associated with Gastrointestinal Disease Presentation

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It has recently been determined that there is an increased prevalence of bacterial overgrowth in IBS. Since there are two gases (hydrogen and methane) measured on lactulose breath testing, we evaluated whether the different gas patterns on lactulose breath testing coincide with diarrhea and constipation symptoms in IBS and IBD. Consecutive patients referred to the gastrointestinal motility program at Cedars-Sinai Medical Center for lactulose breath testing were given a questionnaire to evaluate their gastrointestinal symptoms. Symptoms were graded on a scale of 0–5. Upon completion of the breath test, the results were divided into normal, hydrogen only, hydrogen and methane, and methane only positive breath tests. A comparison of all subjects and IBS subjects was undertaken to evaluate diarrhea and constipation with regards to the presence or absence of methane. This was further contrasted to Crohn's and ulcerative colitis (UC) patients in the database. After exclusion criteria, 551 subjects from the database were available for comparison. Of the 551 subjects ($P < 0.05$, one-way ANOVA) and in a subgroup of 296 IBS subjects ($P < 0.05$, one-way ANOVA), there was a significant association between the severity of reported constipation and the presence of methane. The opposite was true for diarrhea ($P < 0.001$). If a breath test was methane positive, this was 100% associated with constipation predominant IBS. Furthermore, IBS had a greater prevalence of methane production than Crohn's or UC. In fact, methane was almost nonexistent in the predominantly diarrheal conditions of Crohn's and UC. In conclusion, a methane positive breath test is associated with constipation as a symptom.

KEY WORDS: bacterial overgrowth; irritable bowel syndrome; inflammatory bowel disease; methane.

Small intestinal bacterial overgrowth (SIBO) is a condition in which the small bowel is colonized by excessive amounts of upper or lower gastrointestinal tract flora. Although there are many conditions associated with SIBO, recent studies have demonstrated an increased prevalence of SIBO in irritable bowel syndrome (IBS) (1), and it is a recognized cause of diarrhea in inflammatory bowel disease (IBD) (2–4).

One method of diagnosing SIBO is the lactulose breath test (LBT), where overgrowth is considered to be present if a rise greater than 20 ppm in breath hydrogen or methane concentration is observed within 90 min of oral administration of lactulose (5). Hydrogen and methane are common gases excreted during breath testing (6). Although hydrogen production appears more ubiquitous, methane production is seen in 36–50% of healthy subjects (7–9).

Although methane excretion is not present in all individuals, data suggest there may be clinical implications of these different gas profiles. For example, in diarrheal

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conditions such as Crohn's disease (CD) and ulcerative colitis (UC), methane excretion is uncommon (7, 8), whereas it is more prevalent in constipating conditions such as diverticulosis (10) and encoparesis (11). Recently, we reported a double-blind study where the relationship of abnormal lactulose breath test was compared in IBS by treating with an antibiotic (12). In this study, all the subjects with an abnormal breath test consisting of only methane gas production had constipation predominant IBS.

The goal of this study was to confirm and further investigate the relationship between gastrointestinal complaints (specifically, diarrhea and constipation) in IBS subjects with SIBO and gas excretion on LBT in a large prospectively collected database. The prevalence of gas excretion patterns in IBS and the predominantly diarrheal conditions of Crohn's disease and ulcerative colitis will also be compared.

MATERIALS AND METHODS

Patient Population. Consecutive patients referred for a lactulose breath test (LBT) to the Cedars-Sinai Medical Center, GI Motility Program from 1998 to 2000 completed a questionnaire designed to assess bowel symptoms as previously described (1) after approval from the institutional review board. Subjects were requested to rate the severity of nine symptoms (diarrhea, constipation, abdominal pain, bloating, sense of incomplete evacuation, straining, urgency, mucus, and gas) on a scale of 0–5, with 0 signifying the absence of the symptom. The questionnaire also inquired whether subjects had CD or UC. Of subjects reporting a history of IBD, only those whose diagnosis had been confirmed by the Cedars-Sinai Inflammatory Bowel Disease Center were included in the analysis. The diagnosis of IBS was identified if subjects fulfilled Rome I criteria (13). Subjects found to have both IBD and IBS were assigned to the IBD subgroup.

Subjects with conditions predisposing to rapid transit (short bowel syndrome, gastrectomy, etc), those taking narcotic medications, and those without evidence of overgrowth on LBT were excluded.

Lactulose Breath Test (LBT). After an overnight fast, subjects completed the questionnaire. A baseline breath sample was then obtained, after which subjects ingested 10 g of lactulose syrup (Inalco Spa, Milano, Italy, packaged by Xactdose, Inc., South Beloit, Illinois, USA). This was followed by 1 oz of sterile water. Breath samples were then collected every 15 min for 180 min. Each sample was analyzed for hydrogen, methane, and carbon dioxide gas concentration within 15 min of collection using a model SC Quintron gas chromatograph (Quintron Instrument Company, Milwaukee, Wisconsin, USA). CO_2 was analyzed to correct for the quality of the alveolar sampling.

Three abnormal gas patterns were described upon completion of the test: (1) Hydrogen-positive breath test: a rise in breath hydrogen concentration of >20 ppm within 90 min of lactulose ingestion (14–17). (2) hydrogen- and methane-positive breath test: a rise in both breath hydrogen and methane concentrations of >20 ppm within 90 min of lactulose ingestion, and (3) methane-positive breath test: a rise in breath methane concentration of >20 ppm within 90 min of lactulose ingestion.

Data Analysis. For all subjects with SIBO, mean diarrhea and constipation severity scores among the three abnormal gas patterns were compared. Based on symptom severity scores, the entire IBS group was further subdivided into diarrhea-predominant and constipation-predominant subgroups. Constipation-predominant IBS was identified if a subject's constipation severity score exceeded their diarrhea severity score, whereas the reverse applied for diarrhea-predominant IBS. Subjects who had a constipation severity score equal to the diarrhea severity score (indeterminate pattern) were excluded from the IBS subgroup analysis. The percentage of IBS subjects within each abnormal gas pattern who reported constipation-predominant or diarrhea-predominant symptoms was tabulated. The prevalence of methane production between the IBS subgroups was also compared.

Subsequently, a mean C − D score was obtained by calculating the difference between the constipation (C) and diarrhea (D) severity scores. This was used to examine the relative weight of constipation to diarrhea in individual subjects. The C − D score was compared among the three abnormal breath gas patterns in the group as a whole and among IBS subjects.

Finally, the prevalence of each of the three abnormal gas patterns was evaluated in subjects with CD and UC. The prevalence of methane production was contrasted between subjects with IBS and IBD.

Statistical Analysis. A one-way ANOVA was conducted to compare symptom severity scores among the three gas patterns on LBT. Prevalance data was analyzed with a chi-square test.

RESULTS

Subjects. At the time of analysis, 772 patients were referred for a LBT and entered into the database. One hundred eighty-three subjects with negative breath tests and 38 subjects either taking narcotic medications or with conditions predisposing to rapid transit were excluded. A total of 551 subjects remained for analysis. Of these, 78 carried the diagnosis of IBD (49 with CD and 29 with UC) and 296 without IBD fulfilled Rome I criteria for IBS. Of the subjects with IBS, 120 reported constipation-predominant symptoms, 111 had diarrhea-predominant symptoms, and 65 had a constipation severity score equal to the diarrhea severity score.

Bacterial Overgrowth Analysis. When the entire group of subjects with SIBO was evaluated ($N = 551$), the diarrhea severity scores differed significantly among the three abnormal breath test patterns (one-way ANOVA, $P < 0.00001$; Figure 1). Subjects who excreted methane reported significantly lower diarrhea severity scores than those who produced hydrogen only. Constipation severity also differed significantly among the breath test patterns ($P < 0.05$), with higher severity scores reported by subjects who produced methane.

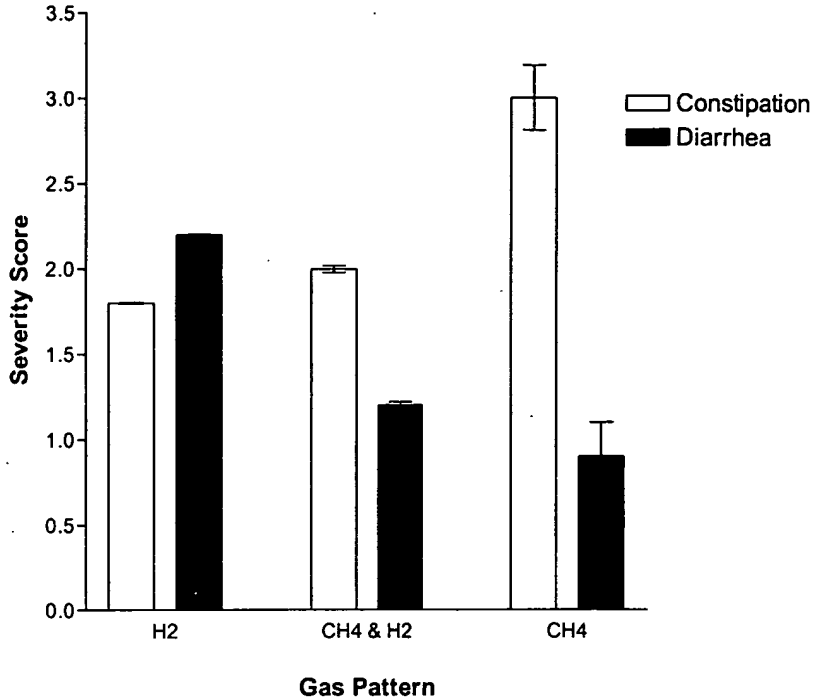

Fig 1. Mean diarrhea and constipation severity scores of all subjects ($N = 551$) with SIBO as a function of the of type of gas pattern produced on LBT. $P < 0.00001$ for trend in reduction of diarrhea with the presence of methane (one-way ANOVA). $P < 0.05$ for the trend towards increasing constipation with the presence of methane (one-way ANOVA).

Among all IBS subjects ($n = 296$), diarrhea severity scores also differed similarly (one-way ANOVA, $P < 0.001$) with a lower severity reported by those who produced methane than those who produced hydrogen gas alone (Figure 2).

When the C-D score was evaluated as a reflection of the degree of constipation with respect to diarrhea, the effect of methane was even more obvious (Figure 3). In both the total group and the IBS subjects, constipation was by far the prevailing symptom in individuals, whereas diarrhea was the prevailing symptom in subjects with only hydrogen.

When IBS subgroups were compared, constipation-predominant IBS was reported by 91 (37%) of the hydrogen-excreting subjects, 23 (52.3%) of the hydrogen- and methane-excreting subjects, and 6 (100%) of the methane-excreting subjects. By contrast, diarrhea-predominant IBS was observed in 105 (42.7%) of the hydrogen excretors, 6 (13.6%) of the hydrogen and methane excretors, and none of the methane excretors (Figure 4).

Inflammatory Bowel Disease and Methane. The predominant gas excreted by patients with IBD was hydrogen alone, detected in 47 of 49 subjects (95.9%) with Crohn's disease and 29 of 29 (100%) of subjects with ulcerative colitis (Figure 5).

Methane Production in Subjects with IBS and IBD. The percentage of subjects with IBS who produced each of the three gas patterns was tabulated. Of 296 IBS subjects, 246 (83.1%) produced hydrogen gas alone, 44 (14.9%) produced hydrogen and methane gas, and 6 (2.0%) produced methane gas alone. Methane production depended significantly upon whether or not subjects had IBS or IBD. IBS subjects were more likely to produce methane gases than subjects with ulcerative colitis or Crohn's disease (OR 7.7, CI 1.8–47.0, $P < 0.01$ Table 1).

DISCUSSION

In this study, we found a significantly higher proportion of breath methane excretion during LBT among subjects with constipation than those with diarrhea. Methane

TABLE 1. COMPARISON OF PREVALENCE OF METHANE TO NONMETHANE GAS PRODUCTION BETWEEN SUBJECTS WITH IBS AND IBD*

Disease type	*CH_4*	*Non-CH_4*
IBS ($N = 296$)	50	246
UC or CD ($N = 82$)	2	76

*$\chi^2 = 9.4$, OR = 7.7, CI: 1.8–47.0, $P < 0.01$.

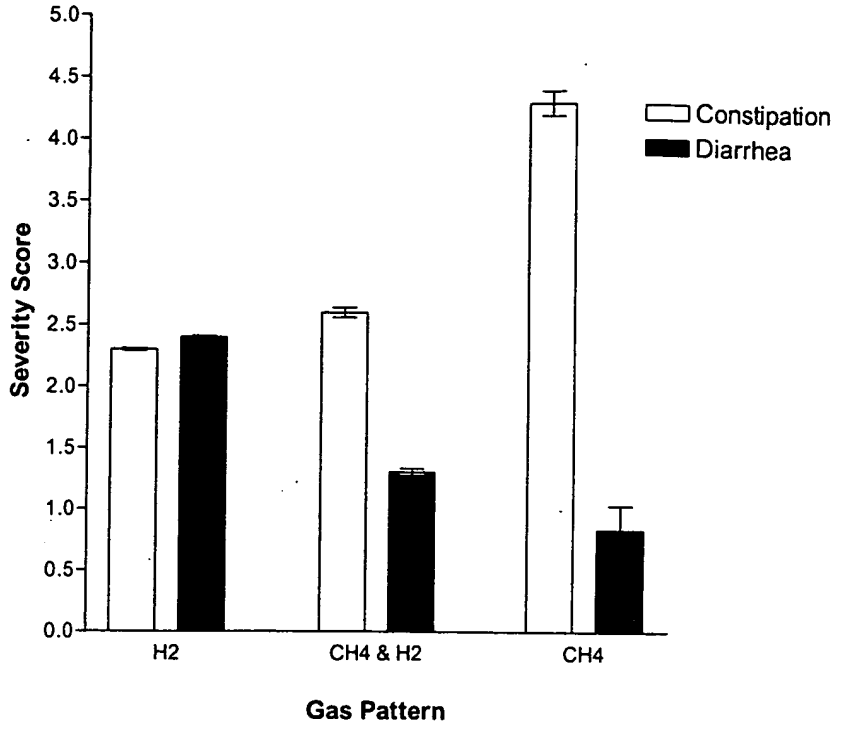

Fig 2. Mean diarrhea and constipation severity scores of IBS subjects ($N = 296$) with SIBO as a function of the of type of gas pattern produced on LBT. $P < 0.001$ for trend in reduction of diarrhea with the presence of methane (one-way ANOVA). $P < 0.05$ for the trend towards increasing constipation with the presence of methane (one-way ANOVA).

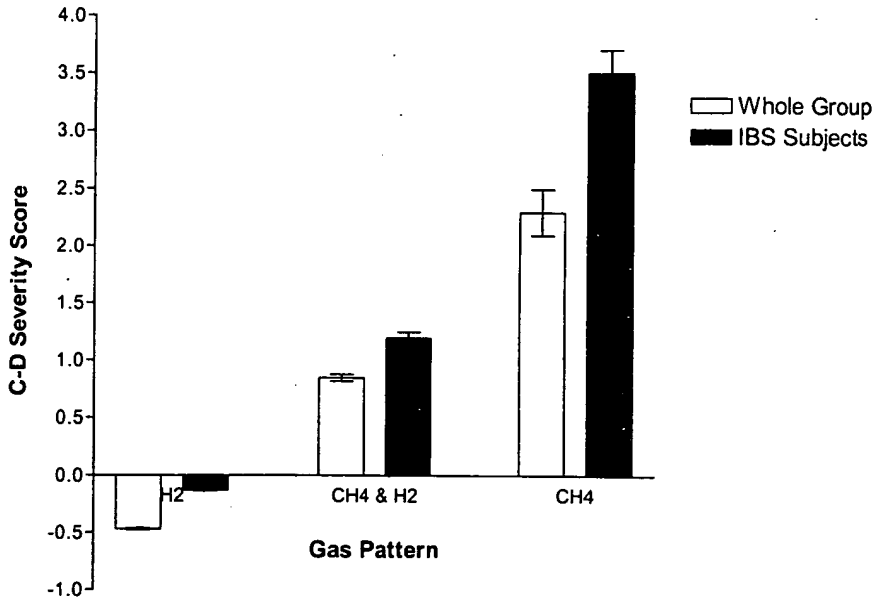

Fig 3. Mean constipation − diarrhea (C − D) severity score for the whole group ($N = 551$) and IBS subjects ($N = 296$) as a function of the type of gas pattern produced on LBT. $P < 0.00001$ for trend in C−D for whole group (one-way ANOVA). $P < 0.0001$ for trend in C−D for IBS subjects (one-way ANOVA).

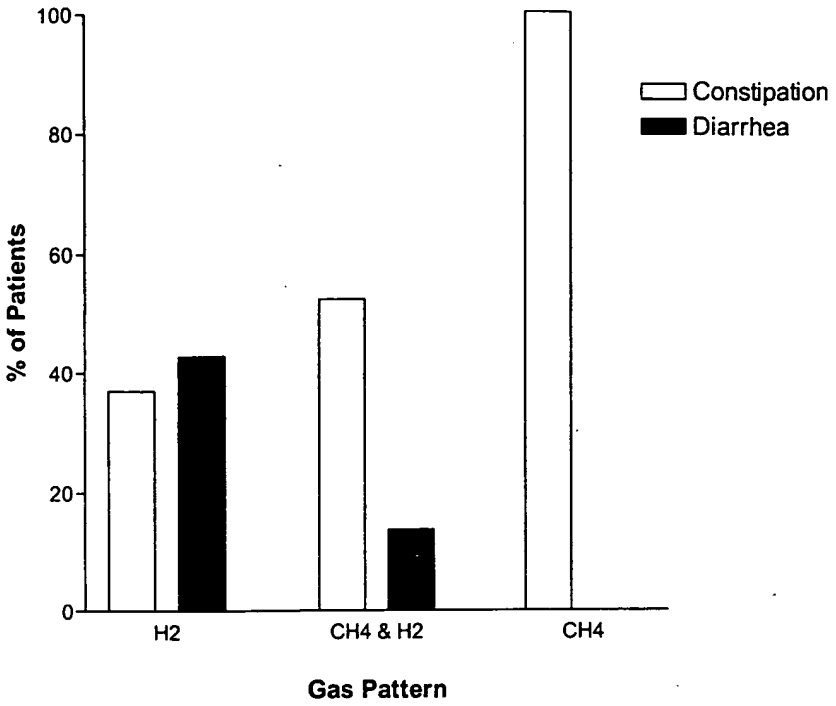

Fig 4. Percentage of IBS subjects within each gas pattern who reported constipation versus diarrhea predominant symptoms. (Chi-square for difference between constipation and diarrhea predominant IBS = 16.6, $P < 0.001$.)

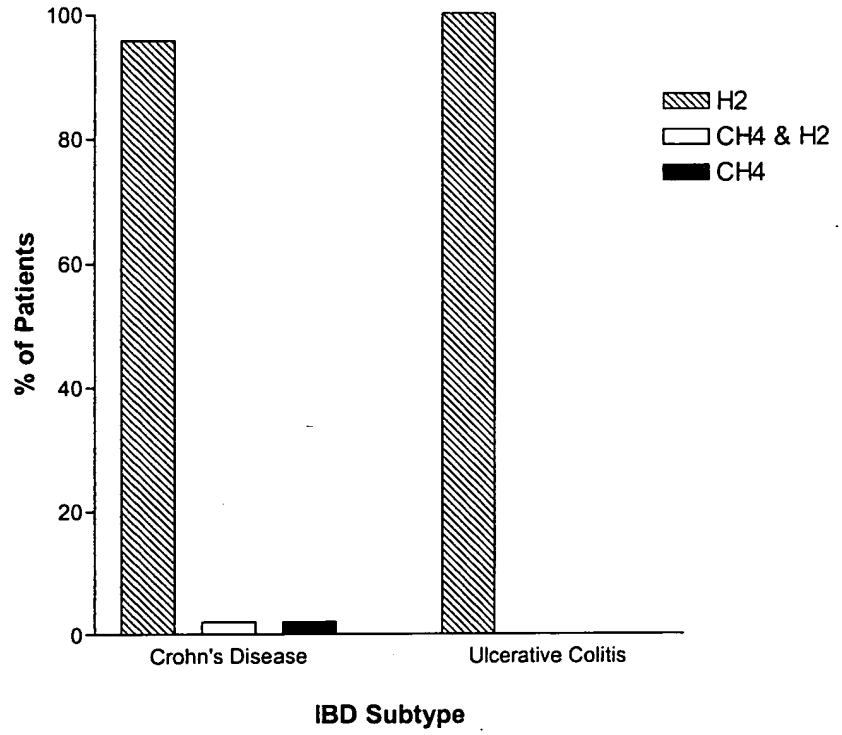

Fig 5. Percentage of subjects with IBD who produced each of the three abnormal gas patterns on LBT.

excretion among subjects with SIBO and IBS was associated with higher constipation severity scores and lower diarrhea severity scores, as well as with the constipation-predominant subgroup of IBS. The findings from this large prospectively collected database continue to support findings similar to a recent study (12). By contrast, methane excretion was infrequent in diarrhea-predominant IBS and virtually absent in IBD.

Relationships between certain gastrointestinal diseases and methane excretion have been described. Previous investigators have observed the prevalence of breath methane excretion to be significantly lower in subjects with diarrheal conditions such as Crohn's disease and ulcerative colitis (7, 8) compared to healthy controls. By contrast, an increased proportion of breath methane excretion has been observed in constipating conditions such as encopresis (11) and high stool concentrations of methanogens have also been found in subjects with diverticulosis (10). The IBS literature is less clear, but one paper suggests an increased prevalence of methane excretion among IBS patients complaining of constipation compared to those who complained of diarrhea (8).

Methane is produced extensively by strict anaerobic bacterial fermentation in the gut and generally has not been found to have a physiologic role in humans (18). Since approximately 20% of colonic methane is excreted via the breath, breath methane analysis has been used as an indirect assessment of intracolonic bacterial metabolism (18). The predominant methanogenic bacteria found in humans is *Methanobrevibacter smithii* (10, 13, 19, 20), which preferentially colonizes the left colon (20–22). It is possible that the lower prevalence of methane excretion in IBD and diarrhea-variant IBS may be an artifact of colonic purging. Diarrhea theoretically may inhibit proliferation of methanogenic bacteria. In support of this hypothesis, colonic lavage can reduce and even eliminate methane excretion for extended periods of time (11). Therefore, one could argue that breath methane may be a marker of constipation.

Another possibility is that the methane production is more proximal in origin. It has been suggested that methane, unlike hydrogen production, does not usually vary with the ingestion of nonabsorbable carbohydrates such as lactulose (18). However, the rise in breath methane excretion we observed upon lactulose ingestion suggests otherwise. Since lactulose would not be expected to reach the left colon (the location of the *Methanobrevibacter smithii*) within 90 mins, other bacteria may be involved in methane excretion in our subjects with small intestinal bacterial overgrowth. For instance, *Clostridia* and *Bacterioides* species are known to liberate methane by using hydrogen produced by regional organisms to reduce carbon dioxide (23). This warrants further investigation, however.

There is further evidence for the role of intestinal gases in symptoms. It has been postulated that the absence of methanogenic flora may be associated with an increase in gastrointestinal complaints (24). Evidence for this relationship derives from studies where patients with lower rates of methanogenesis tend to have higher concentrations of sulfate-reducing bacteria (25–27). The product of bacterial sulfate reduction, hydrogen sulfide, may damage the colonic epithelium. In fact, hydrogen sulfide has been suggested to have a role in the pathogenesis of ulcerative colitis (28, 29). It is known that sulfate-reducing bacteria and methanogenic bacteria compete for hydrogen in the colon via mutually exclusive pathways (26, 27). Thus, if the balance of flora is skewed toward sulfate-reducing bacteria, or if the sulfate-reducing bacteria outcompete the methanogenic bacteria for the available hydrogen substrate needed to support their metabolism, higher concentrations of hydrogen sulfide may be produced, resulting in inflammation and epithelial cell damage. Hydrogen sulfide, however, is not measured by the LBT using current technology.

The observation of methane being associated with constipation in IBS and in general patients with gastrointestinal disease suggests potential therapeutic options. Perhaps altering the balance of organisms to either favor or reduce methanogen populations may benefit subjects with constipation or diarrhea, respectively. Based on this paper, an obvious potential application is in inflammatory bowel disease, whereby observing the effects of administering methanogens may produce benefial results. These potential applications need to be further researched.

In summary, this study demonstrates that the presence of methane on LBT is associated with constipation as a symptom. Likewise, diarrhea and conditions that produce this symptom, such as IBD, are associated with hydrogen production on LBT. Whether the respective gas excretion is simply a marker of symptoms or whether the type of flora causally determines symptoms is as yet unknown.

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Small Intestinal Bacterial Overgrowth: A Possible Association with Fibromyalgia

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ABSTRACT. Objectives: Subjects with fibromyalgia [FMS] frequently have nonspecific bowel complaints similar to subjects with small intestinal bacterial overgrowth [SIBO]. The aim of this study was to test whether 1. SIBO is prevalent in FMS and 2. If treatment of SIBO reduces bowel symptoms.

Methods: Of 815 subjects undergoing lactulose hydrogen breath testing for assessment of SIBO, 123 patients had FMS. Those with SIBO were treated with antibiotics. At the initial and follow-up visits, subjects were asked to rate their symptoms. Symptom scores before and after treatment were compared.

Results: Of the 123 subjects with FMS, 96 [78%] were found to have SIBO. Returning subjects reported a 57 ± 29% overall improvement in symptoms with significant improvement in bloating, gas, abdominal pain, diarrhea, constipation, joint pains, and fatigue [$P < 0.05$].

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Conclusions: 1. Small intestinal bacterial overgrowth is associated with FMS, 2. Eradication of SIBO improves intestinal symptoms in FMS.

KEYWORDS. Bacterial overgrowth, fibromyalgia

INTRODUCTION

Fibromyalgia [FMS] is a chronic condition resulting in soft tissue hyperalgesia. The American College of Rheumatology defines FMS as a history of widespread pain affecting the right and left side of the body for a minimum duration of three months in the setting of 11 out of 18 predefined tender points (1). While FMS is defined by these soft tissue findings, the association of FMS with intestinal symptoms is well known. The common intestinal complaints in FMS include excessive gas, bloating, abdominal pain, and altered bowel habits (2). Some of these symptoms are consistent with irritable bowel syndrome [IBS] so that the lifetime incidence of IBS in subjects with FMS is as high as 52% (3). At the time of presentation, 17% of patients with FMS are already labeled with IBS and 81% of subjects reported irregular bowel habits (2,4). However, even with such strong associations there is no known cause of FMS and its associated intestinal symptoms towards which diagnosis or treatment can be directed.

Small intestinal bacterial overgrowth [SIBO] is a condition where colonic aerobic and anaerobic bacteria are expanded into the small intestine. Since the symptoms of SIBO overlap with the intestinal symptoms of FMS, we tested the hypothesis that SIBO is associated with FMS using a symptom database of patients undergoing a lactulose hydrogen breath test [LHBT]. We also tested the hypothesis that the treatment of SIBO reduces the gastrointestinal symptoms of patients with FMS.

MATERIALS AND METHODS

Consecutive patients referred to the Cedars-Sinai Medical Center Gastrointestinal Motility Program for a LHBT to diagnose SIBO were

given a questionnaire and entered into a database. The questionnaire involved rating intestinal and extraintestinal symptoms such as bloating, gas, diarrhea, constipation, abdominal pain, joint pains, and fatigue on a scale ranging from 0-5, with 0 representing no symptoms. During the LHBT and before the results were available, affected subjects completed the questionnaire both before and after antibiotic treatment. From this database, subjects with FMS were identified on the basis of a past history of this diagnosis. Subjects with a history of inflammatory bowel disease were excluded as these subjects have an increased risk of developing SIBO. In addition, the prevalence of IBS within the group of FMS patients was determined by identifying subjects meeting Rome I Criteria (5).

All subjects diagnosed with SIBO by the LHBT were given a 10 day course of antibiotics by their referring physician [neomycin or ciprofloxacin each at 500 mg po bid or flagyl 500 mg po tid] to eradicate their bacterial overgrowth. Those referred back for a follow-up LHBT approximately 10 days after completion of the antibiotics were given a second questionnaire. Individual symptom ratings from the questionnaire were compared before and after treatment.

RESULTS

The database included 815 subjects. One hundred fifty-two subjects [19%] listed the diagnosis of FMS as part of their medical history. Twenty-nine of the 152 subjects also had inflammatory bowel disease and were excluded, leaving 123 subjects for analysis. Of these 123 subjects, 63 [51%] were referred by a rheumatologist. Of the 63 subjects who were referred by a rheumatologist, 52 [83%] tested positive for SIBO. Twenty-three out of the 123 [19%] subjects had a coexisting connective tissue disease. One hundred seven of the 123 subjects [87%] met Rome I Criteria for IBS. Out of the 123 patients with FMS, 96 tested positive for SIBO [78%] as diagnosed by the LHBT.

Twenty-five patients returned for a follow-up LHBT. Of these subjects, 11 achieved complete eradication and 14 achieved incomplete eradication of their SIBO. The antibiotics used in the treatment of SIBO in the 25 subjects were neomycin [N = 18], augmentin [N = 1], ciprofloxacin [N = 1], flagyl [N = 1], one subject was treated with both neomycin and ciprofloxacin, one was treated with neomycin, biaxin, and amoxicillin, and two subjects did not remember which antibiotics they took. Twenty-two of the 25 FMS subjects returning for follow-up

LHBT reported a 57 ± 29% global improvement in symptoms. The three remaining subjects did not provide a percent global improvement.

The effectiveness of antibiotic treatment was assessed for symptoms and was suggested to be more pronounced when there was complete eradication compared to incomplete eradication [Table 1]. Figure 1 depicts the graded effect of incomplete eradication and complete eradication of SIBO on all symptom scores. The percent decrease of abdominal pain was 68.8 ± 28.8 in the complete eradication group and 1.5 ± 51.0 in the incomplete eradication group [$P < 0.05$ after Bonferroni correction].

On the follow-up questionnaire, patients were also asked to list the symptom[s] most improved. Seventeen patients noted their abdominal complaints improved the most, 7 patients listed pain, 3 fatigue, and 1 reported sleeplessness was most improved.

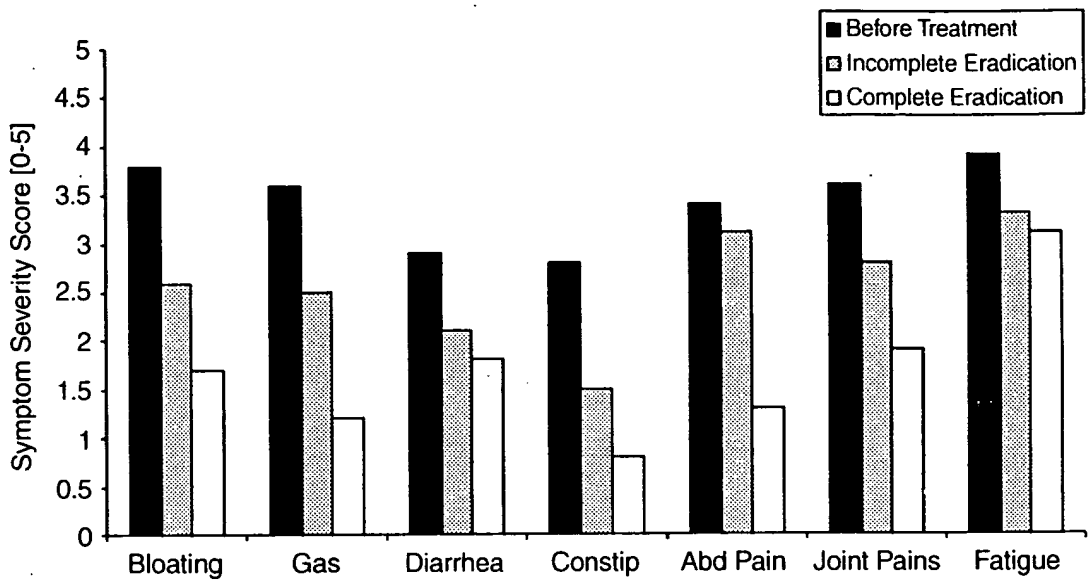
From this data there appears to be an improvement in bowel symptoms after treatment of SIBO in subjects with FMS. Bloating, gas, diarrhea, constipation, and abdominal pain are all improved. More improvement is seen when eradication is complete [Figure 1]. This data suggests that the bowel symptoms in FMS may be caused by SIBO. The causal role of a bacterial agent in FMS has been suggested previously. Links have been proposed between FMS and *Chlamydia* species (6) as well as *Borrelia burgdorferi* (7-9). None of these pathogens has clearly proven to be the causative agent for FMS. From studies in animal models, SIBO does result in bacterial translocation to mesenteric lymph nodes (10-13) and can produce systemic effects. These are believed to be mediated by endotoxin from Gram-negative bacteria (14-16). Such endotoxin related effects

TABLE 1. Visual Analogue Score Symptom Ratings Before and After Treatment in the Incomplete Eradication and Complete Eradication Groups

	Incomplete Eradication				Complete Eradication			
Symptom	N*	Before	After	P-Value†	N*	Before	After	P-Value†
Bloating	11	4.0 ± 1.3	2.6 ± 1.3	< 0.001	10	3.6 ± 1.2	1.7 ± 0.9	< 0.05
Gas	13	3.5 ± 1.6	2.5 ± 1.5	ns	11	3.9 ± 1.5	2.0 ± 1.2	< 0.05
Diarrhea	9	2.6 ± 1.3	1.8 ± 1.8	ns	8	3.3 ± 1.3	1.7 ± 1.2	< 0.05
Constipation	10	2.9 ± 1.6	1.5 ± 1.4	ns	6	2.7 ± 1.6	0.8 ± 1.6	< 0.05
Abdominal pain	12	3.5 ± 1.3	3.1 ± 1.5	ns	8	3.2 ± 1.4	1.3 ± 1.2	< 0.01
Joint pains	13	3.5 ± 1.3	2.8 ± 1.7	ns	8	3.6 ± 1.2	1.9 ± 1.2	< 0.05
Fatigue	13	4.2 ± 0.9	3.3 ± 1.3	ns	10	3.6 ± 1.3	3.1 ± 1.6	ns

*Only subjects who had the symptom were included in the analysis.
†After Bonferroni correction.

FIGURE 1. Symptom score responses to small intestinal bacterial overgrowth treatment.



could explain the soft tissue hyperalgesia seen in FMS since injection of endotoxin in lab animals can result in hyperalgesia (17-24).

In summary, this preliminary study suggests that the intestinal symptoms in FMS may be related to SIBO. Treatment of SIBO in these subjects results in an overall improvement in intestinal symptoms. Further studies using objective measures such as a tender point examination or a scoring system such as the Fibromyalgia Impact Questionnaire (25) to assess the impact of eradication of SIBO on symptoms of FMS are needed. In addition, a double blind study would be of great importance to substantiate the data.

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